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Note

Synthesis of some 6,6′-methylene- and 6,6′-sulphone-biscoumarins

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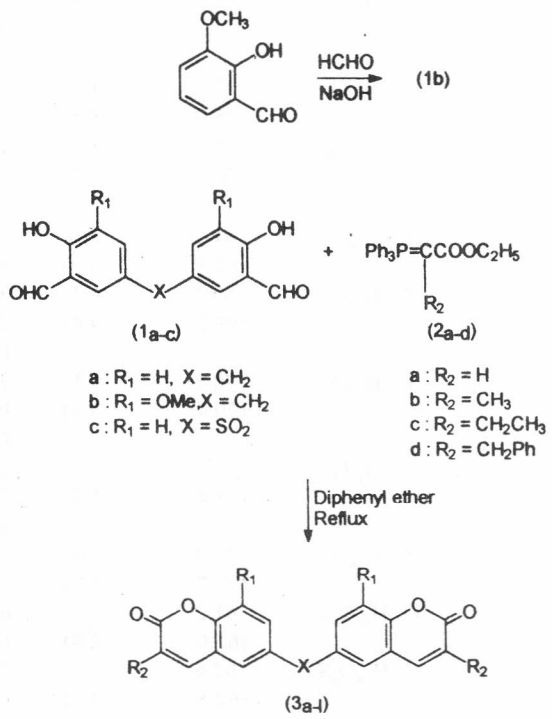
Various 3,3′-disubstituted-6,6′-methylenebiscoumarins **3a-d**, 3,3′-disubstituted-8,8′-dimethoxy-6,6′-methylenebiscoumarins **3e-h** and 3,3′-disubstituted-6,6′-sulphone-biscoumarins **3i-l** have been synthesised by the reaction of appropriate bissalicylaldehydes **1a-c** with (carbethoxyalkylidene)triphenylphosphoranes **2a-d** under Wittig conditions.

Dicoumarol[1] and its derivatives[2,3] which are known for their anticoagulant properties are biscoumarins, in which two coumarin moieties are linked through a methylene bridge. Other biscoumarin derivatives reported in literature are those having phenylene[4], oxygen[5], sulphur[6], etc. as bridge. In all these biscoumarins the two coumarin moieties are joined via their C-3 carbons. Literature survey reveals that the reports on biscoumarins having linkage between two coumarin moieties through their aromatic rings, i.e. via C-5 to C-8 carbon atoms are rare[7,8]. Hence, in the present work various biscoumarins having 6,6′-methylene and 6,6′-sulphone linkages have been synthesised.

Various 3,3′-disubstituted-6,6′-methylenebiscoumarins **3a-d**, 3,3′-disubstituted-8,8′ dimethoxy-6,6′-methylenebiscoumarins **3e-h** and 3,3′-disubstituted-6,6′-sulphone-biscoumarins **3i-l** have been synthesised by reacting the appropriate bissalicylaldehydes **1a-c** with (carbethoxyalkylidene) triphenylphosphoranes **2a-d** under Wittig conditions (Scheme I). Their characterization data are given in Tables I and II. The required 5,5′-methylenebissalicylaldehyde[9] **1a** and 5,5′-sulphonebissalicylaldehyde[10] **1c** were prepared by the methods reported in literature. 3,3′-Dimethoxy-5,5′-methylenebissalicylaldehyde **1b** was prepared from *o*-vanillin and formaldehyde by adopting the method reported for methylenebisvanillin[11]. The reagents (carbethoxyalkylidene)triphenylphosphoranes **2a-d** were also prepared using literature methods[12–14].



Scheme I

Table I—Yields (%) and melting points of biscoumarins **3a-l**

Compd	X	R_1	R_2	mp °C	Yield (%)
3a	CH_2	H	H	200 (lit[7], 201)	57
3b	CH_2	H	CH_3	237	57
3c	CH_2	H	CH_2CH_3	162	53
3d	CH_2	H	CH_2Ph	247	55
3e	CH_2	OMe	H	250	66
3f	CH_2	OMe	CH_3	243	68
3g	CH_2	OMe	CH_2CH_3	160	50
3h	CH_2	OMe	CH_2Ph	180	42
3i	SO_2	H	H	255	62
3j	SO_2	H	CH_3	247	65
3k	SO_2	H	CH_2CH_3	200	55
3l	SO_2	H	CH_2Ph	245	57

Table II—Elemental analyses and spectral data of the biscoumarins **3a-l**

Compd	Mol. formula	Found (%) (Calcd) C	H	^{1}H NMR (δ, ppm)
3a*	$C_{19}H_{12}O_4$	75.3 (75.0	4.0 3.9)	4.1 (2H, s, $-CH_2-$bridge), 6.45 (2H, d, *J*=10 Hz, C_3-H and $C_{3'}$-H, 7.25-7.5 (6H, m, aromatic protons), 7.7 (2H, d, *J*=10 Hz, C_4-H and $C_{4'}$-H)
3b	$C_{21}H_{16}O_4$	75.7 (75.9	4.7 4.8)	2.19 (6H, s, two $-CH_3$), 4.06 (2H, s, $-CH_2$-bridge), 7.18-7.28 (6H, m, aromatic protons), 7.44 (2H, s, C_4-H and $C_{4'}$-H)
3c	$C_{23}H_{20}O_4$	76.8 (76.7	5.3 5.5)	1.24 (6H, t, *J*=6 Hz, two CH_2-CH_3), 2.55 (4H, q, *J*=6 Hz, two CH_2-CH_3), 4.07 (2H, s, $-CH_2$-bridge), 7.15-7.26 (6H, m, aromatic protons), 7.41 (2H, s, C_4-H and $C_{4'}$-H)
3d	$C_{33}H_{24}O_5$	81.7 (81.8	`5.0 4.9)	3.85 (4H, s, two CH_2-Ph), 3.97 (2H, s, $-CH_2$-bridge), 7.08-7.4 (8H, m, aromatic and C_4H and $C_{4'}$-H protons)
3e*	$C_{21}H_{16}O_6$	69.3 (69.2	4.2 4.4)	3.91 (6H, s, two $-OCH_3$), 4.04 (2H, s, $-CH_2$-bridge), 6.42 (2H, d, *J*=10 Hz, C_3-H and $C_{3'}$-H), 6.84-7.25 (4H, m, aromatic protons), 7.61 (2H, d, *J*=10 Hz, C_4-H and $C_{4'}$-H)
3f	$C_{23}H_{20}O_6$	70.5 (70.4	5.3 5.3)	2.18 (6H, s, two CH_3), 3.90 (6H, s, two $-OCH_3$), 4.02 (2H, s, $-CH_2$-bridge), 6.77-7.26 (4H, m, aromatic protons), 7.43 (2H, s, C_4-H and $C_{4'}$-H).
3g	$C_{25}H_{24}O_6$	71.5 (71.4	5.5 5.7)	1.24 (6Hz, t, *J*=6 Hz, two CH_2-CH_3), 2.55 (4H, q, *J*=6 Hz two CH_2-CH_3), 3.9 (8H, s, CH_2-bridge and two $-OCH_3$ merged), 6.79-7.26 (4H m, aromatic protons), 7.42 (2H, s, $-C_4$-H and $C_{4'}$-H)
3h	$C_{35}H_{28}O_6$	77.3 (77.2	5.0 5.1)	3.89 (12H, s, two $-OCH_3$ and all benzylic protons merged), 6.67-7.29 (16H, m, aromatic protons and C_4-H and $C_{4'}$-H)
3i	$C_{18}H_{10}O_6S$	61.2 (61.0	2.7 2.8)	6.52 (2H, d, *J*=10 Hz, C_3-H and $C_{3'}$-H), 7.2-8.2 (8H, m, aromatic protons and C_4-H, $C_{4'}$-H)
3j	$C_{20}H_{14}O_6S$	62.6 (62.8	3.5 3.7)	2.24 (6H, s, two CH_3), 7.27-8.06 (8H, m, aromatic protons and C_4-H, $C_{4'}$-H)
3k	$C_{22}H_{18}O_6S$	64.5 (64.4	4.2 4.4)	1.21 (6H, t, *J*=6 Hz, two CH_2-CH_3 protons), 2.57 (4H, q, *J*=6 Hz, two $-CH_2-CH_3$), 7.26-8.2 (8H, m, aromatic protons and C_4-H, $C_{4'}$-H)
3l*	$C_{32}H_{22}O_6S$	71.7 (71.9	4.4 4.1)	3.88 (4H, s, two $-CH_2$-Ph), 7.18-8.1 (18H, m, aromatic protons and C_4-H, $C_{4'}$-H).

IR: 1720 (δ-lactone) and 2940 cm^{-1} ($-CH_2-$) for **3a, 3c, 3e** and **3f**; 1730 (δ-lactone) and 2930 ($-CH_2-$) for **3b**; 1710 (δ-lactone) and 2940 ($-CH_2-$) for **3d**.

*The mass spectra of compounds **3a, 3e** and **3l** showed the molecular ion peaks (M^+) at m/z 304, 364 and 535, respectively.

Experimental Section

General. IR spectra were recorded in KBr on a Perkin-Elmer 983 spectrophotometer (ν_{max} in cm^{-1}), and ^{1}H NMR spectra in $CDCl_3$ on a Hitachi R-1500, 60 MHz spectrophotometer using TMS as internal standard (chemical shifts in δ, ppm). Mass spectra of three compounds (**3a**, **3e** and **3l**) were recorded on a Finnigan GC/MS.

Preparation of 3,3′-dimethoxy-5,5′-methylene-bissalicylaldehyde 1b. A mixture of *o*-vanillin (17.8 g, 0.117 mole) and 37% formalin (5.5 mL, 0.064 mole) was heated at 100°C for 15 min. A solution of sodium hydroxide (0.125 mole) in 5 mL of water was added slowly with stirring to the above hot mixture and the heating continued for additional 30 min. The reaction mixture was poured into 250 mL hot water and 50 mL 10% HCl was added to it. The yellow solid product separated out was filtered, washed with hot water, dried, and re-crystallised from chloroform, yield 54%, m.p. 156-58°C. Anal. Calcd for $C_{17}H_{16}O_6$: C, 64.5; H, 5.0. Found: C, 64.7; H, 5.2%; IR: 2940 (C–H stretching of $-CH_2-$), 1650 (–C=O stretching of aldehyde); ^{1}H NMR: 3.88 (6H, s, two $-OCH_3$), 4.00 (2H, s,$-CH_2-$), 6.90 (4H, s, aromatic protons), 9.95 (2H, s, two –OH), 10, 90 (2H, s, two –CHO).

Synthesis of 6,6′-methylene- and 6,6′-sulphone-biscoumarins 3a-l: General procedure. To a mixture of bissalicylaldehyde **1** (0.0025 mole) and (carbethoxyalkylidene) triphenylphosphorane **2** (0.0075 mole) was added diphenyl ether (10 mL) and the reaction mixture refluxed on a sand-bath

for 4 hr, allowed to cool to room temperature and petroleum ether (60-80°C) (50 mL) added to it. A solid product separated out in case of **3a-d** which was triturated with 50 mL of solvent ether to remove triphenylphosphine oxide formed. Compounds **3e-l** separated out as gummy mass, which was extracted with chloroform. The chloroform extract was washed with water, dried, chloroform removed and the residue upon column chromatography over silica gel using ethyl acetate-benzene (2:8) as an eluent furnished **3e-l**.

All the compounds were recrystallised from chloroform-hexane. The % yield and mp's are given in Table I, while elemental analyses and spectral data are furnished in Table II.

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